A New, Facile Synthesis of 4-Alkyl- and Aryl-Substituted 3-Amino-4*H*-1,2,4-benzothiadiazine 1,1-Dioxides

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A new efficient preparation of 4-alkyl- and aryl-substituted 3-amino- 4*H*-1,2,4-benzothiadiazine 1,1-dioxides **(3)** is described via the 3-chloro derivatives of 4-alkyl- and aryl substituted 3-oxo-2*H*-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides **(1)** on their treatment with aqueous ammonia solution.

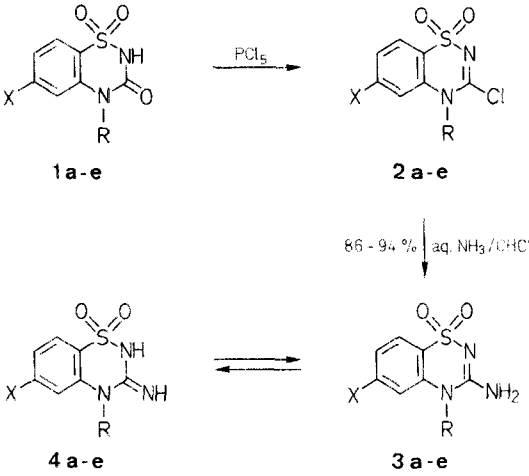
The 1,2,4-benzothiadiazine 1,1-dioxide class of heterocycles have attracted considerable interest on account of their biological properties, particularly after the discovery of Diazoxide[1], an antihypertensive agent. We have been interested in the preparation of 4-substituted 3-amino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides **(3)** as intermediates in the synthesis of new fused heterocycles[2] derived from 1,2,4-benzothiadiazine 1,1-dioxide.

It is reported[3] that attempts to prepare 3-amino-6-chloro-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide **(3b)** by fusion of guanidine carbonate with 4-chloro-2-methylaminobenzene sulfonamide were unsuccessful, while condensation of 4-chloro-2-aminobenzene sulfonamide and guanidine carbonate afforded 6-chloro-3-amino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (yields 18–53%) which on methylation gave 3-amino-6-chloro-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide[3] in 60% yield. Reported syntheses of the title compounds[4,5] are very tedious, involving the separation of isomers (i.e., 2 and 4-substituted intermediates) and the amination of 3-methylthio-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide by ammonium carbonate in a sealed tube. Further, the yields are low and involve various reaction steps.

Table. 4-Alkyl- and Aryl-Substituted 3-Amino-4*H*-1,2,4-benzothiadiazine 1,1-Dioxides (**3a–e**)

Product	R	X	Yield [%]	m.p. [°C] (Lit. m.p.)	Molecular Formula[a]	M.S. (70 eV) *m/e* (M^+)	IR (KBr) ν [cm^{-1}]
3a	CH_3	H	90	316–318	$C_8H_9N_3O_2S$ (211.2)	211	3380, 3330, 3230 1645, 1270, 1150
3b	CH_3	Cl	93	276–278 (275–278)[3]	$C_8H_8ClN_3O_2S$ (245.7)	245	3385, 3325, 3235, 1645, 1270, 1150
3c	C_2H_5	H	92	240–241	$C_9H_{11}N_3O_2S$ (225.3)	225	3400, 3320, 3240, 1640, 1280, 1160
3d	*i*-C_3H_7	H	86	282–283	$C_{10}H_{13}N_3O_2S$ (239.3)	239	3390, 3320, 3235, 1640, 1280, 1165
3e	C_6H_5	H	94	299–300	$C_{13}H_{11}N_3O_2S$ (273.3)	273	3400, 3320, 3230, 1645, 1275, 1160.

[a] Satisfactory microanalyses obtained: C ±0.25, H ±20, N ±0.15.



Herein, we report a new facile method for the synthesis of 4-alkyl- and aryl-substituted 3-amino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (**3**) an important intermediate of biological significance from 4-alkyl- and aryl-substituted 3-chloro-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (**2**) by treatment with ammonia (25% solution). Intermediates **2**[6] are obtained by the reaction of 4-alkyl- and aryl-substituted 3-oxo-2*H*-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides[7] (**1**) with phosphorus pentachloride. It is reported[8] that the chlorine atom of 3-chloro-6-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide is relatively inert; we found, however, that the chlorine atom in 4-substituted 3-chloro-4*H*-1,2,4-benzothiadiazine 1,1-dioxides **2** is extremely reactive.

The yields of **2** and **3** are very high (86–94%). The IR spectra of compounds **3** show a strong band between 1640–1645 cm^{-1}, characteristic of the C=NH group[9], thus revealing that **3** exists in the tautomeric form **4**. The results are summarized in the Table. The experimental simplicity makes the present method a convenient and efficient method of synthesis for the title compounds.

3-Amino-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (3a); Typical Procedure:

To a solution of 3-chloro-4-methyl-4H-1,2,4-benzothiadiazine 1,1-dioxide (**2**; 2.3 g, 0.1 mol) in chloroform (25 ml) at room temperature is added aqueous ammonia solution (10 ml, 25%, sp.gr. 0.91) dropwise with stirring over a period of 5 min. Vigorous stirring is continued for an additional 5 min. The colorless precipitate is filtered, washed with water (50 ml), and recrystallized from ethanol-water.

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[1] Rubin, A.A., Roth, F.E., Winbury, M.M. *Nature* **1961**, *192*, 176.
[2] Reddy, A.V.N., Kamal, A., Rao, A.B., Sattur, P.B. *Eur. J. Med. Chem. Chim. Ther.* **1986**, *21*, 177.
[3] Topliss, J.g., Konzelman, L.M. *J. Org. Chem.* **1963**, *28*, 2313.
[4] Raffa, L., Di Bella, M., Melegari, M., Vampa, G. *Farmaco Ed. Sci.* **1962**, *17*, 331; *C.A.* **1963**, *55*, 19945.
[5] Raffa, L., Melegari, M., Vampa, G. *Farmaco Ed. Sci.* **1966**, *21*, 839; *C.A.* **1967**, *67*, 3281.
[6] Reddy, A.V.N., Kamal, A., Sattur, P.B. *Ind. J. Chem.* **1985**, *24B*, 1295.
[7] Girard, Y., Atkinson, J.G., Rokach, J. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1043.
[8] Landquist, J.K. in: *Comprehensive Organic Chemistry*. Barton, D., Vol.4, Sammes, P.G., Ed., Pergamon Press, Oxford, 1979, p. 1115.
[9] Witkop, B. *J. Am. Chem. Soc.* **1956**, *78*, 2873.